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Letter to the Editor

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Letter to the Editor (Other)

Minimal added value of separate dryness assessments compared with overall dryness in ESSPRI in patients with Sjögren's disease

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Rheumatology key message

- Separate dryness assessments add minimal value to the overall dryness question included in the ESSPRI.

Dear Editor, Sjögren's disease (SjD) is characterized by severe sicca complaints, primarily of eyes and mouth, although patients can also experience other sicca symptoms such as vaginal or cutaneous dryness. To assess patients' symptoms, the European Alliance of Associations for Rheumatology (EULAR) Sjögren's Syndrome Patient Reported Index (ESSPRI) was developed in 2011 [1]. This validated patient-reported outcome measure (PROM) is the mean of three questions regarding patients' symptoms of overall dryness, fatigue and pain in the past 2 weeks, scored on a numeric rating scale (NRS) from 0 to 10 [2]. In the development study, overall dryness showed the highest correlation with patient global disease activity (GDA) compared with most of the dryness questions for each anatomical location separately. Recently, two novel composite endpoints have been developed for use in clinical trials, the Composite of Relevant Endpoints for Sjögren's Syndrome (CRESS) [3] and the candidate Sjögren's Tool for Assessing Response (STAR) [4]. Both endpoints consist of five clinically relevant items for SjD, including ESSPRI as PROM item. However, it has been questioned whether the overall dryness question included in the ESSPRI is sufficient to capture the whole spectrum of dryness symptoms in SjD. Therefore, the objective of this study was to analyse whether separate dryness assessments could be of added value to the ESSPRI in patients with SjD.

Baseline data of 302 SjD patients fulfilling 2016 American College of Rheumatology (ACR)/EULAR classification criteria and with available ESSPRI data in the Registry of Sjögren Syndrome LongiTudinal (RESULT) cohort [5] of the University Medical Centre Groningen were used. PROMs collected in the RESULT cohort were: ESSPRI, NRS scores for oral, ocular and vaginal dryness, the Xerostomia Index (XI) questionnaire [6], Ocular Surface Disease Index (OSDI) questionnaire [7] and patient GDA. Furthermore, baseline data of 28 SjD patients who participated in a rituximab trial were used since this trial included a different set of dryness PROMs: ESSPRI overall dryness and NRS scores for oral, ocular, cutaneous, nasal, tracheal and vaginal dryness [8]. Spearman's correlation coefficient was used to assess the association of overall dryness with other dryness PROMs and patient GDA. A correlation coefficient of <0.2 was interpreted as poor, 0.2–0.4 as fair, 0.4–0.6 as moderate, 0.6–0.8 as good and >0.8 as excellent. For the RESULT cohort data, univariable linear regression with overall dryness as dependent variable was performed to assess the association with other dryness PROMs. Multivariable linear regression using the enter method was performed to test whether the adjusted R^2 improved when adding multiple dryness PROMs to the model.

Baseline characteristics of the included SjD patients from the RESULT cohort and rituximab trial are shown in Supplementary Table S1, available at *Rheumatology* online. In Fig. 1A, a correlation matrix is shown of the PROMs analysed in the RESULT cohort. Of all dryness PROMs, overall dryness showed the highest association with patient GDA ($\rho = 0.58$, $P < 0.001$). Oral dryness showed the highest association with overall dryness ($\rho = 0.82$, $P < 0.001$), followed by ocular dryness ($\rho = 0.67$, $P < 0.001$). These results were confirmed by the stronger association of the XI compared with OSDI with overall dryness. In univariable linear regression, oral dryness also showed the highest explained variance ($R^2 = 0.67$) for overall dryness (Supplementary Table S2, available at *Rheumatology* online). When adding ocular dryness to the multivariable model, the adjusted R^2 improved to 0.75. When adding vaginal dryness (including only females), the explained variance did not change ($R^2 = 0.75$) (Supplementary Table S3, available at *Rheumatology* online).

In Fig. 1B, a correlation matrix is shown of the dryness PROMs analysed in the rituximab trial. Of all separate

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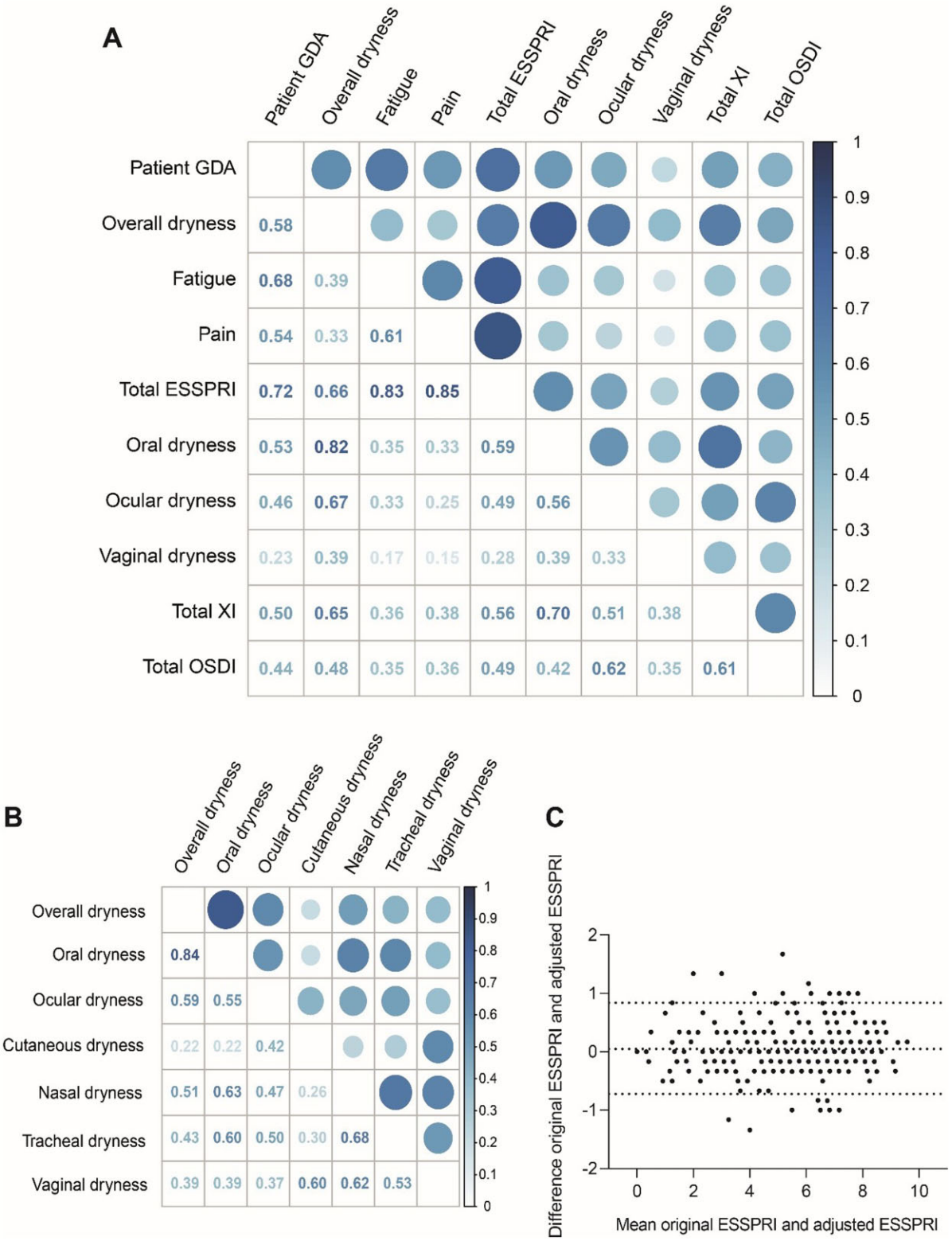

Figure 1. (**A**) Correlation matrix of dryness PROMs and patient GDA in SjD patients at baseline from the RESULT cohort. (**B**) Correlation matrix of dryness PROMs at baseline from the rituximab trial. (**C**) Bland–Altman plot of the original ESSPRI total score and the ESSPRI total score in which the overall dryness question was replaced by the mean of oral and ocular dryness NRS scores (adjusted ESSPRI) of SjD patients from the RESULT cohort and rituximab trial. ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index; GDA: global disease activity; OSDI: Ocular Surface Disease Index; PROM: patient-reported outcome measure; RESULT: Registry of Sjögren Syndrome LongiTudinal; SjD: Sjögren's disease; XI: Xerostomia Index

dryness questions, the highest association with overall dryness was found for oral dryness ($\rho = 0.84$, $P < 0.001$), followed by ocular dryness ($\rho = 0.59$, $P < 0.001$).

Next, combining RESULT cohort and rituximab trial data, we replaced the overall dryness question in the ESSPRI by the mean of oral and ocular dryness, and found an excellent

correlation between the original and adjusted ESSPRI total scores ($\rho = 0.97$, $P < 0.001$). A Bland–Altman plot for the original ESSPRI total score and the ESSPRI including the mean of oral and ocular dryness showed that the mean difference between both scores was very close to 0 (0.06). The 95% limits of agreement were −0.72 to 0.84, which fall within the validated definition of minimal clinically important improvement of ≥1 point (Fig. 1C).

Based on our analyses in a large group of SjD patients from daily clinical practice as well as a smaller group of SjD patients with active disease in a trial, overall dryness included in the ESSPRI is a relevant and accurate dryness PROM. Oral and ocular dryness were the most important dryness features determining the overall patient-reported dryness, compared with other separate dryness questions. Replacing the ESSPRI overall dryness question by the mean of oral and ocular dryness yielded very similar results, suggesting that it is sufficient to rate only symptoms of overall dryness in the ESSPRI in SjD patients.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

Data are available from the University of Groningen-UMCG Institutional Data Access for researchers who meet the criteria for access to confidential data. The local ethics committees of the University Medical Center Groningen (UMCG) will maintain the ethical restrictions of the data. The Data Protection Officer of the UMCG will maintain the legal restrictions and appropriate codes of conduct. Permission is required prior to access. Data requests can be sent to Research Data Office University of Groningen: researchdata@rug.nl.

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Ethics: The RESULT cohort and rituximab trial were approved by the local ethics committee of the UMCG (RESULT: METc 2014/491, rituximab trial: METc 2008/179). All patients provided written informed consent according to the Declaration of Helsinki.

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